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Blood Cadmium and Depressive Symptoms in Young Adults (20-39 years)

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Abstract

Background—Genetic and environmental factors contribute to the risk of depression and several studies have noted an association between tobacco smoke and depression. Cadmium is a neurotoxicant, and the main source of non-occupational exposure is tobacco smoke.

Methods—We conducted a cross-sectional analysis of data from 2892 young adult (20-39 years) participants of the National Health and Nutrition Examination Survey (NHANES) 2007-2010. Multivariate logistic regressions – adjusted for age, sex, race/ethnicity, education, poverty-income ratio, obesity, alcohol intake, blood lead, and smoking status – were used to analyze the association between blood cadmium and depressive symptoms, as determined by score on the PHQ-9.

Results—Individuals in the highest quartile of blood cadmium had higher odds of having depressive symptoms (OR=2.79; 95% CI, 1.84, 4.25) compared to those in the lowest blood cadmium quartile. Smoking status was statistically significantly associated with depressive symptoms while blood lead was not. Stratification by smoking status found that blood cadmium was significantly associated with depressive symptoms in both non-smokers (OR=2.91; 95% CI, 1.12, 7.58) and current smokers (OR=2.69; 95% CI, 1.13, 6.42).

Conclusions—This is the first study reporting an association of blood cadmium levels with depressive symptoms using a nationally representative sample. The association of cadmium with depressive symptoms was independent of smoking status. If this association is further confirmed, the continued efforts at reducing cadmium exposures, mainly through tobacco smoking cessation programs, may decrease the incidence of depression.

INTRODUCTION

Depression is a common mental disorder and a major cause of illness and disability worldwide (Kessler & Bromet 2013). Depression is among the leading causes of decreased work productivity (Stewart et al. 2003). The estimated prevalence of depression among U.S. adults is currently 9.1% (http://www.cdc.gov/features/dsdepression/index.html#reference).

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Both genetic and environmental factors contribute to the risk of depression (Lanni et al. 2009).

Individuals with depression as well as mental illness in general have a higher rate of cigarette smoking. However, the association between tobacco smoking and depression seems to be bidirectional. On one hand, there is evidence suggesting cigarette smoking increases the risk of depression (Aubin et al. 2012; Boden et al. 2010; Weaver & Etzel 2003) on the other hand, increased cigarette smoking may be a result of self-medication (Crone & Reijneveld 2007; Lerman et al. 1998; Pomerleau & Pomerleau 1992). Tobacco and tobacco smoke contain over 8,400 chemical constituents (Rodgman & Perfetti 2008). Among the compounds found in tobacco smoke are lead, which has been associated with major depression (Bouchard et al. 2009), and cadmium, which has neurotoxic properties (ATSDR 2012).

Cadmium is a non-essential carcinogenic metal that occurs in the earth's crust and is commonly associated with zinc, lead, and copper ores and is a natural constituent of ocean water (ATSDR 2012). Cadmium is released into the atmosphere via natural and anthropogenic sources with emissions from anthropogenic sources greatly exceeding those of natural origin. Major industrial sources of cadmium emissions include zinc, lead, copper, and cadmium smelting operations, coal and oil-fired boiler, phosphate fertilizer manufacture – a major source of cadmium input to agricultural soil, and municipal and sewage sludge incinerators. Cadmium bioaccumulates at all levels of the food chain, with the highest levels found in leafy vegetables, such as lettuce and spinach, potatoes, grains, peanuts, and organ meats such as liver and kidney. Additionally, cadmium naturally accumulates in large amounts in tobacco leaves. Cadmium-containing products including nickel-cadmium batteries, jewelry, toys, and electronic devices are another important source of exposure. Among the routes of exposure, inhalation is the predominant route of exposure for the smoking general population and for occupational populations, whereas oral exposure is the predominant route of exposure for the nonsmoking general population. Dermal exposure plays a minor role in exposure for the general population. Cadmium toxicity affects several organs including kidney, lung, liver and brain (ATSDR 2012).

Cadmium association with neurobehavioral effect was found in occupational studies (Hart et al. 1989; Viaene et al. 2000), as well as in animal studies (Ali et al. 1990; Baranski 1984; Goncalves et al. 2012; Leret et al. 2003). Cadmium exposure was associated with learning disabilities and lower neuropsychological test scores in children (Capel et al. 1981; Ciesielski et al. 2012; Stellern et al. 1983)). A statistically significant increase of serum cadmium and lead was also found in patients with depression compared to healthy age- and sex-matched controls (Stanley & Wakwe 2002).

Based on this evidence of a possible association between cadmium and neurobehavioral outcomes we decided to analyze a large representative sample of U.S. young adults, 20-39 years of age, from the National Health and Nutrition Examination Survey (NHANES) to determine whether blood cadmium is associated with depressive symptoms. To our knowledge, this is the first study reporting on the association of blood cadmium levels with depressive symptoms using a nationally representative sample.

METHODS

Study population

NHANES is a cross-sectional, nationally representative survey of the non-institutionalized civilian population of the United States conducted by the National Center for Health Statistics, CDC (NCHS 2008a). Beginning in 1999, the survey has been conducted continuously and released in 2-year cycles. For our study we merged the publicly available files for NHANES cycles 2007-2008, and 2009-2010 using the NCHS recommendations (NCHS 2008b). The survey employs a multistage stratified probability sample based on selected counties, blocks, households, and persons within households.

NCHS-trained professionals conducted interviews in participants' homes, and extensive physical examinations, including blood collection, were conducted at mobile exam centers (MECs). CDC's National Center for Environmental Health (NCEH), Division of Laboratory Sciences (DLS) coordinates the National Biomonitoring Program (NBP) which offers an assessment of nutritional status and the exposure of the U.S. population to environmental chemicals and toxic substances.

All procedure were approved by the NCHS Research Ethics Review Board (Continuation of Protocol #2005-2006 http://www.cdc.gov/nchs/nhanes/irba98.htm), and all participants provided written informed consent. The unweighted response rate for participants aged 20-39 years for NHANES 2007-2008 and NHANES 2009-2010 were 75.2% and 78.1%, respectively (http://www.cdc.gov/nchs/nhanes/response_rates_CPS.htm). For our analysis, we focused on young adult (ages 20-39 years) participants (n=3,785) in order to minimize conditions such as osteoporosis, which mobilizes cadmium and lead from the bone thus increasing their levels in the blood. Pregnant women were excluded. Of the participants who answered the Patient Health Questionnaire (PHQ)-9 module (n=3,316), we included only those participants who had measurements for blood lead and blood cadmium (n=3,169). Additionally, participants with missing information on *a priori* covariates were excluded from our analysis for a total sample size of 2,892 participants.

Outcome

The outcome was the presence or absence of depressive symptoms, as determined by score on the PHQ-9, a self-administered version of the depression module of the Primary Care Evaluation of Mental Disorders Questionnaire (PRIME-MD). PHQ-9 contains 9 questions that were used as a depression screener in NHANES 2007-2008 and 2009-2010. These are based on the 9 signs and symptoms for depression listed in the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV). Responses to these 9 questions were on a 4-point Likert scale of 0 to 3, indicating that the participant experienced the symptom "not at all," "on several days," "on more than half the days," or "nearly every day" during the past 2 weeks for a total score ranging from 0 to 27. For our sample, the scores ranged from 0-25, with a median value of 2, a 95th percentile of 13, and less than 10% having scores ≥ 10. A prior validation study found that a score ≥10 achieved 88% sensitivity and 88% specificity for major depression (Kroenke et al. 2001). Therefore, a participant who scored 10 or more was defined as having depressive symptoms. This cut-off has been validated for

the general population (Kocalevent et al. 2013) and has been applied in other NHANES studies (Golub et al.2010)

Covariates

Whole blood cadmium (BCd) and blood lead (BPb) concentrations were measured using inductively-coupled plasma mass spectrometry by CDC's National Center for Environmental Health (NCEH), Division of Laboratory Sciences (DLS). Detailed methodology and QA/QC instructions are discussed in the NHANES Laboratory Procedures Manual (http://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/PbCd_E_met_lead_cadmium.pdf; http://www.cdc.gov/NCHS/data/nhanes/nhanes_09_10/PbCd_F_met.pdf)

Blood cadmium was categorized by weighted quartile (Q) distribution. A total of 833 participants had BCd values below the limit of detection (LOD 2007–2012: 0.20μg/l); therefore, these participants were considered the referent lowest cadmium quartile (BCdQ1). The cutpoints for the other BCd quartiles were as follows: BCdQ2 0.20-0.27μg/L; BCdQ3 0.28-0.54 μg/L; and BCdQ4 >0.54 μg/L. Blood lead was categorized by weighted quartiles: BPbQ1 ≤ 0.63μg/dL; BPbQ2 0.64-0.90μg/dL; BPbQ3 0.91-1.36 μg/dL; BPbQ4 >1.36 μg/dL.

The regression models were adjusted for covariates that are associated with depression: age (categorized in weighted quartile), sex, race/ethnicity, education, poverty income ratio, obesity, alcohol consumption, smoking status, and blood lead. We obtained information about age (years), gender, race/ethnicity, and education from the household interview. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic, and other. Poverty income ratio (PIR) is a measure of socioeconomic status and represents the calculated ratio of household income to the poverty threshold after accounting for inflation and family size. Body Mass Index (BMI) is calculated by the weight divided by height squared (kg/m^2). The adult population was classified as overweight and obese with BMI measures of 25-29.9 and ≥30 kg/m^2, respectively.

Alcohol consumption (amount consumed per week) and smoking information were obtained from the associated questionnaire. Cigarettes smoking was defined as non-smoker (smoke < 100 cigarettes ever), former smoker (not currently smoking, but has smoked ≥100 cigarettes ever), and current smoker. Serum cotinine is a biomarker of secondhand smoke (SHS) and was categorized as: low exposed non-smoker (serum cotinine below detection limit); high exposed non-smokers (serum cotinine levels below or equal to 3.0 ng/mL); and exposed smokers (serum cotinine >3.0 ng/mL). The cutoff of 3.0 ng/mL to define active smoking was derived from Benowitz and colleagues (Benowitz et al.2009). Therefore, to avoid information bias due to self-reported cigarette smoking, we used both self-reported cigarette use and serum cotinine cutoff to define smoking status: smokers included self-reported current smokers and those with serum cotinine levels ≤ 3.0 ng/mL and non-smokers included self-reported former and never smokers and those with serum cotinine levels ≤ 3.0 ng/mL. Former smokers were included with never smokers because the BCd levels were similar (geometric mean [GM] = 0.25μg/L and 0.22 μg/L, respectively), whereas current smokers had a higher BCd level (GM = 0.76 μg/L). Moreover, the use of SHS and self-

reported smoking status as independent variables in the model did not change the association between cadmium and depressive symptoms.

Statistical Methods

MEC exam sample weights were used for analyses to account for the complex sampling design and non-response of NHANES. Weights for combined NHANES survey cycles were calculated according to NHANES guidelines (NCHS 2008b). We estimated sampling errors using the Taylor series linearized method. We used logistic regression to calculate adjusted odds. SAS 9.3 (SAS Institute, Cary, NC) was used for all statistical analyses and SAS-Callable SUDAAN 10 (Research Triangle Institute, Research Triangle Park, NC) was used to account for the NHANES complex sample design. We also assessed possible interactions between cadmium and sex, but because the interaction was not statistically significant, it was not included in the models. P-values from Satterthwaite statistics were presented at the significance level < 0.05.

RESULTS

Table 1 presents the characteristics of the study population. The geometric mean age was similar in both men and women (data not shown). The geometric mean BCd level was 0.31 μg/L. Blood cadmium geometric mean for women was (0.33 μg/L) and for men was (0.30 μg/L) (data not shown). The number of individuals with depressive symptomswas 287 (weighted percentage 7.85%). Table 2 shows the characteristics of depressive symptom cases and controls by covariates used in the models. Depressive symptoms were statistically significantly higher in women, in individuals with lower PIR, in those with less than high school education, in obese individuals, and in smokers. Additionally, depressive symptoms were significantly associated with s blood cadmium.

Logistic regression analysis adjusting for age, sex, race/ethnicity, education status, PIR, obesity, alcohol consumption, blood lead and smoking status showed that the highest BCd quartile was significantly associated with higher odds of having depressive symptoms (OR= 2.79; 95% CI: 1.84, 4.25; p-value for trend = 0.001) compared to the referent lowest BCd quartile (Table 3). Analyses using continuous log natural-transformed cadmium confirmed the statistically significant association (data not shown).

Higher odds to have depressive symptoms was statistically significantly associated with current smoking status (OR = 1.54; 95% CI: 1.00, 2.36) compared to non-smokers, whereas blood lead levels were not statistically significantly associated (data not shown). Since cigarette smoking is related to cadmium exposure, we conducted a stratified analysis based on smoking status. We found that the highest quartile of BCd was statistically significantly associated with depressive symptoms both in non-smokers (OR = 2.91; 95% CI: 1.12, 7.58) and in current smokers (OR = 2.69; 95% CI: 1.13, 6.42) compared to the referent BCd quartile (Table 3).

DISCUSSION

To our knowledge, this is the first study reporting an association of blood cadmium levels with depressive symptoms using a nationally representative sample.

Compared with persons with blood cadmium level less than 0.20 μg/L those with a level greater than 0.47 μg/L had a 2.8-fold increased risk of having depressive symptoms. Furthermore, after stratification by smoking status, the association of BCd with depressive symptoms persisted in both current smokers and non-smokers; therefore, the association of cadmium with depressive symptoms is not likely to be confounded by smoking or other compounds present in the cigarette smoking such as cotinine and lead.

Bouchard and colleagues (2009) previously reported an association between blood lead and major depression among young adult (20-39 years of age) participants in NHANES 1999-2004. In our study using NHANES 2007-2010, BPb was not associated with depressive symptoms. Similarly, Golub and colleagues (2010) did not find an association between BPb and depression in adults aged 20 years and older participating in the NHANES 2005-2006 cycle. These differences may be due to the decrease of blood lead that occurred in the last decades or to residual confounding.

There is a strong association between smoking and depression; however, this link may be bidirectional – depression increases the risks of smoking (Crone & Reijneveld 2007; Lerman et al. 1998; Pomerleau & Pomerleau 1992), and smoking increases the risks of depression (Aubin et al. 2012; Boden et al. 2010; Weaver & Etzel 2003). Studies conducted among non-smoking adults suggest that exposure to SHS is correlated with depression (Bandiera et al. 2010; Nakata et al. 2008); whereas, other studies fail to find such an association (Bot et al. 2013; Lam et al. 2013). In this study, among individuals not currently smoking, we did not find any association between serum cotinine and depressive symptoms (data not shown). However, there was an association between cadmium and depressive symptoms among those not currently smoking. This suggests that cadmium, whether from SHS or diet in non-smokers, may be a contributing risk factor to depression.

The biological plausibility of our findings is unclear because of the scarcity of studies pertaining to cadmium exposure and neurobehavioral outcomes. Studies in rats have shown that cadmium can increase the permeability of the blood brain barrier, which can lead in the brain to intracellular cadmium accumulation and cell dysfunction in adult rats (Goncalves et al. 2010; Mendez-Armenta & Rios 2007). Impairment in the monoaminergic neurotransmission system is associated with the depression and anxiety disorder (Lanni et al. 2009), and cadmium may contribute to the etiology of depression through perturbation of the catecholamine/serotonin system. Adult male rats exposed to cadmium show a decreased content of serotonine, dopamine and norepinephrine in all brain regions (Lafuente et al. 2001, 2003). Other experimental studies on rats indicate that early exposure to cadmium can induce behavioral and neurotoxic effects, including a decrease of locomotor activity or an increase of anxiety-like behavior (Ali et al. 1990; Baranski 1984; Leret et al. 2003). Gonçalves and colleagues (2012) reported an impaired cognition and enhanced anxiety-like behavior associated with increased acetylcholinesterase activity and a decrease of Na^+, K^+-

ATPase activity in pubertal male rats treated with cadmium in the diet. Studies of exposed children show that high cadmium concentrations in hair are associated with learning difficulties (Capel et al. 1981; Ciesielski et al 2012).

One of the strengths of the present study is the use of the structured self-report assessment PHQ-9, which is widely used in psychiatric research and has a high degree of correspondence with clinical interviews (Martin et al. 2006). The present study has several limitations, the most important being its cross-sectional design, which limits the inferences that can be made based on the findings. Medical conditions such as osteoporosis, during which cadmium and lead are released from the bone matrix to the blood may affect our findings. However, in this study few individuals were likely to have osteoporosis because of their young age (maximum age of 39 years). Blood cadmium is considered a biomarker for recent, short-term exposure; however, it was found that cadmium in blood is composed of a short half-life of 3-4 months (Jarup et al. 1983). The latter is reflective of the cadmium body burden; therefore, blood cadmium may be a good indication of long-term low-level exposure (Jarup et al. 1998). The depression status in our study is limited to answers in the PHQ-9 about the experience of the participants during the past 2 weeks, so the so the presence of depressive symptoms reflect a current status. Therefore, blood cadmium (as a biomarker of recent exposure) may be appropriate to use in this case.

The association reported in this study could be biased by uncontrolled confounders such as genetic predisposition (Cohen-Woods et al. 2013). However, the models were adjusted for several likely important confounding factors (sex, age, race/ethnicity, education status, annual income, obesity, alcohol, smoking status, serum cotinine and blood lead). Although the possibility that depression leads to behavioral changes that increase exposure to cadmium (i.e. tobacco smoke) cannot be ruled out, the result among current nonsmokers may propose otherwise. Analyses that included only non-smokers indicate that residual confounding by smoking does not explain the associations of BCd levels and risks of depression, and that cadmium may be an independent risk factor of depression.

If cadmium exposure is associated with depression, continued efforts at reducing cadmium population exposures mainly through tobacco smoking cessation programs, which have the added benefit of decreased cadmium exposure through second- and third-hand smoke, may help decrease the population incidence of depression A recent meta-analysis reported that smoking cessation is associated with reduced depression (Taylor et al. 2014), findings that may help to overcome professional reluctance to intervene with smokers who have mental health problems (Chang et al. 2011; Johnson et al. 2010). Given that cadmium is associated with several chronic diseases (ATSDR 2012), the benefits of smoking cessation are multifold by decreasing both the incidence of smoking-related diseases as well as cadmium-associated diseases

However, further studies, such as well-designed prospective studies to evaluate the effect of cadmium exposure and the risk of developing depression are needed to more fully understand the implications of the findings of this study.

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TABLE 1

Sample size (N) and weighted characteristics of young adults participants in NHANES 2007-2010

	ALL	
	N	**Weighted**
Blood Cadmium (μg/L), GM (SE)	2892	0.31 (0.01)
Blood Lead (μg/dL), GM (SE)	2892	0.96 (0.02)
Age (Years), GM (SE)	2892	28.93 (0.34)
BMI(kg/m^2), GM (SE)	2892	27.32 (0.18)
Serum Cotinine (ng/mL), GM (SE)	2892	0.75 (0.11)
Sex		
Men, % (SE)	1439	51.38 (1.05)
Women, % (SE)	1453	48.62 (1.05)
Depressive Symptoms		
Yes, % (SE)	287	7.85 (0.44)
No, % (SE)	2605	92.15 (0.44)
Body Weight		
Underweight/Normal weight, % (SE)	1044	38.18 (1.58)
Overweight, % (SE)	861	29.89 (0.89)
Obese, % (SE)	987	31.93 (1.45)
Poverty Income Ratio		
PIR (below or equal poverty line), % (SE)	794	19.84 (1.18)
PIR (above poverty line), % (SE)	2098	80.16 (1.18)
Smoking Status		
Current Smokers (self-report and LBXCOT>3.00 ng/mL), % (SE)	1093	37.15 (1.52)
Not-Current Smoker (Self-report Former and never smoker and lbxcot≥3ng/mL), % (SE)	1799	62.85 (1.52)
Alcohol Consumption		
No Alcohol, % (SE)	615	18.31 (0.95)
1-4 drinks per week, % (SE)	1826	66.70 (1.51)
>4 drinks per week, % (SE)	451	14.99 (1.11)
Education Level		
Less than High School, % (SE)	670	17.37 (1.14)
Completed High School, % (SE)	689	21.89 (1.18)
More than High School, % (SE)	1533	60.74 (1.90)
Race/ethnicity		
White (Non-Hispanic), % (SE)	1306	63.24 (2.92)
Non-Hispanic Black, % (SE)	527	11.59 (1.19)
Hispanic, % (SE)	896	18.12(2.21)
Other, % (SE)	163	7.05 (0.82)
Blood Cadmium Quartile		
BCd Q1 (Below limit of detection 0.20 μg/L), % (SE)	833	31.44 (1.12)
BCd Q2 (0.20 – 0.27 μg/L), % (SE)	640	22.19 (0.92)
BCd Q3 (0.28 – 0.54 μg/L), % (SE)	719	23.74 (0.97)

	ALL	
	N	**Weighted**
BCd Q4 (>0.54 μg/L), % (SE)	700	22.63 (1.36)
Blood Lead Quartile		
BPb Q1 (≤ 0.63 μg/dL), % (SE)	661	24.75 (1.16)
BPb Q2 (0.64 – 0.90 μg/dL), % (SE)	734	25.39 (1.23)
BPb Q3 (0.91 – 1.36 μg/dL), % (SE)	712	25.00 (0.86)
BPb Q4 (>01.36 μg/dL), % (SE)	785	24.86 (1.30)
Age Quartile		
Age Q1 (20 - 24 years), % (SE)	743	25.55 (1.40)
Age Q2 (25 – 29 years), % (SE)	669	25.78 (1.28)
Age Q3 (30 – 34 years), % (SE)	717	22.54 (0.88)
Age Q4 (35 – 39 years), % (SE)	763	26.13 (0.89)

TABLE 2

Chi Square analyses between depressive symptoms cases and controls in young adults (aged 20-39 years) in NHANES 2007-2010.

	Depressive symptoms		
	Case, n	**Control, n**	**χ^2 p value**
Sex			
Men	94	1345	<.001
Women	193	1260	
Race/Ethnicity			
Non-Hispanic White	119	1187	
Non-Hispanic Black	62	465	.04
Hispanic	95	801	
Other	11	152	
Age quartile			
AgeQ1 (20 - 24 years)	68	675	
AgeQ2 (25 – 29 years)	58	611	
AgeQ3 (30 – 34 years)	68	649	.09
AgeQ4 (35 – 39 years)	93	670	
Education level			
Less than High School	102	568	
Completed High School	71	618	.002
More than High School	114	1419	
Poverty Income Ratio			
PIR≤1	131	663	<.001
PIR > 1	156	1942	
OBESITY			
Underweight/Normal	88	956	
Overweight	74	787	.002
Obese	125	862	
Alcohol consumption			
No Alcohol	64	551	
1-4 drinks per week	172	1654	.46
>4 drinks per week	51	400	
Smoking Status			
Current Smokers (self-report and LBXCOT>3.00 ng/mL)	163	930	
Not-Current Smoker (Self-report Former and never smoker and lbxcot≥3ng/mL	124	1675	<.001
Blood Cadmium Quartile			
BCd Q1 (Below limit of detection 0.20 μg/L)	53	780	
BCd Q2 (0.20 – 0.27 μg/L)	44	596	<.001
BCd Q3 (0.28 – 0.54 μg/L)	61	658	
BCd Q4 (>0.54 μg/L)	129	571	
Blood Lead Quartile			

	Depressive symptoms		
	Case, n	**Control, n**	**χ^2 p value**
BPb Q1 (≤ 0.63 μg/dL)	66	595	
BPb Q2 (0.64 – 0.90 μg/dL)	76	658	.96
BPb Q3 (0.91 – 1.36 μg/dL)	76	636	
BPb Q4 (>01.36 μg/dL)	69	716	

Table 3

Adjusted* ORs (95% CIs) of depressive symptoms by blood cadmium levels in young adults (aged 20-39 years) in NHANES 2007-2010

	All Participants *	Non-smokers*	Current Smokers*
Cadmium			
BCd Q1 (Below limit of detection 0.20 μg/L)	1.00	1.00	1.00
BCd Q2 (0.20 – 0.27 μg/L),	1.04 (0.58, 1.87)	1.28 (0.65, 2.55)	0.63 (0.27, 1.45)
BCd Q3 (0.28 – 0.54 μg/L),	1.11 (0.70, 1.76)	1.26 (0.71, 2.25)	1.02 (0.36, 2.94)
BCd Q4 (>0.54 μg/L)	2.79 (1.84, 4.25)	2.91 (1.12, 7.58)	2.69 (1.13, 6.42)
p trend	0.001	0.28	<0.001

* Adjusted for age, sex, race/ethnicity, education, PIR, obesity, alcohol intake, blood lead, and smoking status (defined as current smoker: self-report and LBXCOT>3.00 ng/mL; and non-smoker: Self-report Former and never smoker and lbxcot≥3ng/mL)